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TITLE: Gene delivery system and methods of use

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CLAIMS:

What is claimed is:

1. A recombinant replication competent retrovirus comprising:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope;

an oncoretroviral polynucleotide sequence comprising Long-Termal Repeat (LTR) sequences at the 5' and 3' end of the oncoretroviral genome, wherein a tissue-specific promoter sequence is contained within the U3 region of the LTR sequence at the 5' or 3' or 5' and 3' end of the oncoretroviral polynucleotide sequence,

a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence; and

cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell.

2. The retrovirus of claim 1, wherein the oncoretroviral polynucleotide sequence from an oncoretrovirus selected is from the group consisting of murine leukemia virus (MLV), Moloney murine leukemia virus (MoMLV), Gibbon ape leukemia virus (GALV) and Human Foamy Virus (HFV).

3. The retrovirus of claim 2, wherein the MLV is an amphotropic MLV.

4. The retrovirus of claim 1, wherein the retroviral envelope comprises a chimeric protein.

5. The retrovirus of claim 4, wherein the chimeric protein comprises an ENV protein and a targeting polypeptide.
6. The retrovirus of claim 5, wherein the ENV protein is selected from the group consisting of a murine leukemia virus (MLV) ENV protein and vesicular stomatitis virus (VSV) ENV protein.
7. The retrovirus of claim 5, wherein the targeting polypeptide is an antibody, a receptor, or a receptor ligand.
8. The retrovirus of claim 5, wherein the ENV protein is an amphotropic protein.
9. The retrovirus of claim 5, wherein the ENV protein is an ecotropic protein.
10. The retrovirus of claim 1, wherein the target cell is a cell having a cell proliferative disorder.
11. The retrovirus of claim 1, wherein the target cell is a neoplastic cell.
12. The retrovirus of claim 10, wherein the cell proliferative disorder is selected from the group consisting of lung cancer, colon-rectum cancer, breast cancer, prostate cancer, urinary tract cancer, uterine cancer lymphoma, oral cancer, pancreatic cancer, leukemia, melanoma, stomach cancer and ovarian cancer.
13. The retrovirus of claim 1, wherein the promoter sequence is operably linked with a growth regulatory gene.
14. The retrovirus of claim 1, wherein the heterologous polynucleotide sequence is a suicide gene.
15. The retrovirus of claim 14, wherein the suicide gene encodes a thymidine kinase.
16. The retrovirus of claim 1, wherein the heterologous sequence is a marker gene.
17. The retrovirus of claim 1, wherein the regulatory nucleic acid sequence operably linked with the heterologous nucleic acid sequence is selected from the group consisting of a promoter, an enhancer, and an internal ribosome entry site.
18. A recombinant retroviral polynucleotide, comprising:
 - a polynucleotide sequence encoding a GAG protein;
 - a polynucleotide sequence encoding a POL protein;
 - a polynucleotide sequence encoding a retroviral envelope;
 - a polynucleotide sequence derived from an oncoretrovirus comprising a Long Terminal Repeat (LTR) at the 5' and 3' end of the retroviral polynucleotide sequence wherein a target-specific promoter sequence is contained within the U3 region of the LTR sequences at the 5' and 3' or 5' and 3' end of the retroviral polynucleotide;
 - a heterologous polynucleotides sequence operably linked to a regulatory nucleic acid sequence; and
 - cis acting polynucleotide sequence necessary for reverse transcription,

packaging and integration in a target cell.

19. The polynucleotide of claim 18, wherein the GAG, POL and retroviral envelope polynucleotide sequences are derived from murine leukemia virus (MLV) or Moloney murine leukemia virus (MoMLV).

20. The polynucleotide of claim 19, wherein the MoMLV is an amphotropic MoMLV.

21. The polynucleotide of claim 20, wherein the polynucleotide sequence encoding a retroviral envelope encodes a chimeric protein.

22. The polynucleotide of claim 21, wherein the chimeric protein comprises an ENV protein and a targeting polypeptide.

23. The polynucleotide of claim 22, wherein the ENV protein is selected from the group consisting of a murine leukemia virus (MoMLV) ENV protein and Vesicular stomatitis virus (VSV) ENV protein.

24. The polynucleotide of claim 22, wherein the targeting polypeptide is an antibody, a receptor, or a receptor ligand.

25. The polynucleotide of claim 23, wherein the ENV protein is an amphotropic protein.

26. The polynucleotide of claim 23, wherein the ENV protein is an ecotropic protein.

27. The polynucleotide of claim 18, wherein the target cell is a neoplastic cell.

28. The polynucleotide of claim 18, wherein the target cell has a cell proliferative disorder.

29. The polynucleotide of claim 28, wherein the cell proliferative disorder is selected from the group consisting of lung cancer, colon-rectum cancer, breast cancer, prostate cancer, urinary tract cancer, uterine cancer lymphoma, oral cancer, pancreatic cancer, leukemia, melanoma, stomach cancer, thyroid cancer, liver cancer, and brain cancer and ovarian cancer.

30. The polynucleotide of claim 18, wherein the promoter sequence is associated with a growth regulatory gene.

31. The polynucleotide of claim 18, wherein the heterologous polynucleotide sequence is a suicide gene.

32. The polynucleotide of claim 31, wherein the suicide gene encodes a thymidine kinase or a purine nucleoside phosphorylase (PNP).

33. The polynucleotide of claim 18, wherein the heterologous sequence is a marker gene.

34. The polynucleotide of claim 18, wherein the regulatory nucleic acid sequence operably linked with the heterologous nucleic acid sequence is selected from the group consisting of a promoter, an enhancer, and an internal ribosome entry site.

35. The polynucleotide of claim 18, wherein the polynucleotide sequence is contained in a viral particle.

36. The polynucleotide of claim 18, wherein the polynucleotide sequence is contained in a pharmaceutically acceptable carrier.

37. A recombinant replication competent murine leukemia virus (MLV), comprising:

an MLV GAG protein;

an MLV POL protein;

an MLV envelope;

an MLV polynucleotide sequence comprising Long-Termal Repeat (LTR) sequences at the 5' and 3' end of the retroviral genome, wherein a target-specific promoter sequence is contained within the LTR sequences at the 5' and 3' end of the MLV polynucleotide sequence,

a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence; and

cis-acting nucleic acid sequences necessary for reverse transcription, packaging and integration in a target cell.

38. A recombinant replication competent retrovirus comprising:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope comprising a chimeric env protein comprising a targeting ligand;

an oncoretroviral polynucleotide sequence comprising Long-Termal Repeat (LTR) sequences at the 5' and 3' end of the oncoretroviral polynucleotide sequence, wherein a tissue-specific promoter sequence is contained within the U3 region of the LTR sequences at the 5' or 3' or 5' and 3' end of the oncoretroviral polynucleotide sequence,

a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence; and

cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell.

39. A recombinant retroviral polynucleotide, comprising:

a polynucleotide sequence encoding a GAG protein;

a polynucleotide sequence encoding a POL protein;

a polynucleotide sequence encoding a retroviral envelope, wherein said envelope comprises a chimeric env protein comprising a targeting ligand;

a polynucleotide sequence derived from an oncoretrovirus comprising a Long Terminal Repeat (LTR) at the 5' and 3' end of the retroviral polynucleotide, wherein a tissue-specific promoter sequence is contained within the U3 region of the LTR sequences at the 5' or 3' or 5' and 3' end of the retroviral polynucleotide;

a heterologous polynucleotide sequence operably linked to a regulatory nucleic acid sequence; and

cis acting polynucleotide sequence necessary for reverse transcription, packaging and integration in a target cell.

